FUNCTIONAL CONTRIBUTIONS OF ELECTRICAL SYNAPSES IN SENSORY AND MOTOR NETWORKS

Lidia Szczupak


szczupak@retina.ar
Abstract

Intercellular interactions in the nervous system are mediated by two types of dedicated structural arrangements: electrical and chemical synapses. Several characteristics distinguish these two mechanisms of communication, such as speed, reliability and the fact that electrical synapses are, potentially, bidirectional. Given these properties, electrical synapses can subserve three main interrelated network functions: signal amplification, noise reduction and/or coincidence detection. Specific network motifs in sensory and motor systems of invertebrates and vertebrates illustrate how signal transmission through electrical junctions contributes to a complex processing of information.
Introduction

Intercellular communication in the nervous system is mediated by two types of dedicated structural arrangements: electrical and chemical synapses (e-Syns and ch-Syns, respectively). It is well documented that e-Syns play a major role during development of the nervous system and that this intercellular communication, although to a smaller degree, persists in the adult nervous systems of invertebrates and vertebrates [1-6]. Growing amount of data have established that e-Syns play definite circuit functions in adult networks. This review focuses on specific network configurations at which e-Syns play substantial physiological roles.

Structural properties of electrical synapses

While the structure of ch-Syns is in itself asymmetric (pre and postsynaptic terminals have differential structures and roles), e-Syns exhibit a symmetric structure. Each one of the interconnected cells presents ionic channels that are precisely aligned to channels in the other cell, forming a pathway for direct flow of small molecules (< 1 kD) and current from one cell to the other [7]. This intercellular communication is not particular of the nervous system as it is also present in the vast majority of animal tissues, and receives the generic name of gap junctions (GJs).

GJs play highly similar physiological roles in invertebrates and vertebrates and, consistently, bear highly similar structural characteristics. However, no homology was found between the proteins forming GJs in these two subphyla [8]. GJs are formed by innexins in the invertebrates [9] and by connexins in the vertebrates [10]. Twenty five innexins have been identified in C. elengans [11], twenty one in leeches [12] and nine in Drosophila [13]; using the nervous system of locust four innexins were found [14], and six in crabs [15]. In mammals twenty connexins have been characterized [16].

Innexin and connexin proteins exhibit four membrane-spanning regions. In vertebrates the three-dimensional structure of GJs has been extensively studied and the reports indicate that each hemichannel is a hexameric polypeptide [7]. A recent structural analysis performed in C. elegans found that each hemichannel in this nematode is an octameric polypeptide [17]. It remains to be established if this is a particular case or a general property of the invertebrate GJs.
**Functional properties of electrical synapses**

Several characteristics distinguish e-Syns and ch-Syns: (i) the delay between pre and postsynaptic signals is significantly shorter in e-Syns; (ii) e-Syns are more reliable than stochastic ch-Syns [18]; and (iii) e-Syns are potentially symmetrical, where pre and postsynaptic sites are interchangeable, depending on which is the emitter (presynaptic) and which is the receiver (postsynaptic) at any instant.

GJs are considered and modeled as electrical resistors [19-21]. Therefore it is expected that transmission through e-Syns is reproduced consistently upon repetitive stimulation, and that the postsynaptic response is a lower amplitude version of the presynaptic signal. Because GJs are usually located at the neurites [22-25] signal transmission is subjected to the characteristic low-pass filter imposed by their cable properties [26-30]. In turn, the amplitude of the postsynaptic response is heavily dependent on the frequency components of the presynaptic signal.

In addition, the presence of voltage-activated conductances in the membrane associated with GJs can strongly influence the amplitude and dynamics of the transmitted signal [31-34].

Although potentially symmetrically bidirectional (ohmic), e-Syns can also rectify: the conductance of the GJ depends on the polarity of the transjunctional potential [the difference between the membrane potential (Vm) at each side of the GJ] [35]. This implies that, close to their resting potential, the transmission of depolarizing or hyperpolarizing signals is transmitted best in one direction (cell A ⇒ cell B) than in the other (cell B ⇒ cell A) [36-39].

Rectification can be a property of the GJs, but it also can result from the differential intrinsic properties of the interconnected neurons or from coexistence of e-Syns and ch-Syns linking pairs of neurons [40,41].

**Electrical synapses in the context of functional networks**

Given these properties, e-Syns can subserve three main interrelated network functions: signal amplification, noise reduction and/or coincidence detection. The following are examples where these functions are achieved in the context of sensory and motor networks.
**Electrical synapses in sensory systems.**

Sensory systems are organized to maximize sensitivity and acuity. Lateral inhibition has been described as an important network mechanism, mediated mostly by ch-Syns, to improve acuity [42,43] while lateral excitation has been proposed as a mechanism to increase sensitivity. GJs are a common feature of lateral excitatory networks.

The connection between primary auditory afferents and the Mauthner cells, that command the startle reflex in teleosts, is mediated by e-Syns and ch-Syns (Figure 1.A). Upon the stimulation of one terminal, depolarization of the Mauthner cell can exert a fast retrograde depolarization of other afferents through the e-Syns, causing an amplification of the input to the command neuron [44].

A classical example of lateral excitation is found in the mechanosensory activation of the crayfish lateral giant neurons that command the tailflip escape response. The sensory neurons are interconnected by ohmic e-Syns and are linked to the command neuron by rectifying e-Syns (higher conductance when $V_{m_{afferents}} > V_{m_{command}}$) (Figure 1.B). This network was proposed as a mechanism to amplify the response within a restricted window of time, as inputs to a few afferents can instantaneously spread to others and increase the response of the command neuron [22,45,46]. An equivalent mechanism has been recently described in *C. elegans* [47,48] and in the mesencephalic nucleus of mammals [32].

In the visual system of blowflies, a set of motion-sensitive (tangential) cells of the lobula plate process information in separate retinotopically arranged columns, and project to higher brain centers. Because neighbor tangential cells are electrically coupled (Figure 1.C), each cell exhibits a broader receptive field than expected from the anatomy and connectivity of their respective dendritic trees [49,50]. Physiological and modeling studies indicate that this connectivity pattern confers the tangential cell population the capability of generating a linear integration of the visual input [51] and the spread of signals throughout the e-Syns exert a key role in this integration [52].

The vertebrate retina is another classical example where lateral excitation between different types of neurons subserves amplification and improves signal-to-noise ratio. Photoreceptors are relatively noisy elements and their electrical coupling promotes a decrease of uncorrelated noise and a relative amplification of correlated
visual signals, at the expense of certain degree of blurring [53,54]. E-Syns are not limited to the receptor layer but are vastly expressed among different neurons in the retina [55,56].

In the olfactory system of insects, peripheral receptor neurons reach the antennal lobe, where they contact projection neurons that transmit excitatory signals to higher centers. Peripheral receptors expressing a specific odorant receptor make ch-Syns with projection neurons in discrete regions of the antennal lobe called glomeruli. Projection neurons innervating the same glomerulus (“sister projection neurons”) are linked by ohmic e-Syns that provide for signal amplification [57] (Figure 1.D).

Projection neurons receive input from excitatory and inhibitory local interneurons that span across several glomeruli (Figure 1.D). Excitatory interneurons and projection neurons are bidirectionally connected: while transmission from excitatory interneurons to projection neuron is mediated by e-Syns, transmission in the opposite direction is mediated by ch-Syns [57,58]. This horizontal pathway is interpreted as a mechanism to amplify and speed up odor detection at low odorant levels, at the expense of specificity. Additional interglomerular interactions are mediated by a subset of inhibitory projection neurons that connect to uniglomerular projection neurons by ch-Syns and e-Syns introducing another layer of horizontal interactions [59].

The olfactory system of vertebrates presents several homologies with that of insects. Mitral cells (analogous to the projection neurons) in the olfactory bulb receive inputs from receptor neurons and project the processed information to higher brain regions. Odor-specific mitral cells project to the same glomerulus, and are interconnected by e-Syns and ch-Syns that grant their synchronic firing [23,60]. Studies performed in zebrafish show that inhibitory interneurons in the olfactory bulb are linked to mitral cells by e-Syns and ch-Syns modulating their activity in a bidirectional fashion. These synaptic interactions boost responses to weak stimuli and attenuate responses to strong stimuli. Boosting of weak inputs depends on electrical coupling, whereas attenuation of strong inputs is probably caused by ch-Syns [61]. This network action equalizes the mean population response of mitral cells favoring a concentration-invariant identification of odors.
**Electrical synapses in motor control**

Motor behaviors are controlled by hierarchical systems. Higher levels determine global aspects of behaviors while premotor networks at the lowest level are organized into distinct modules that configure sets of movements [62-64]. Studies at the premotor level established that e-Syns subserve a variety of distinct functions.

In several invertebrate systems MNs are interconnected by e-Syns [15,65-69]. A similar picture was observed in the vertebrates [70-73]. Electrical coupling among MNs that innervate synergistic muscles [1,67] can be simply interpreted: synchronous activation of MNs can grant a more precise phasing of muscle activity. However, e-Syns could be widespread [74] and expressed among MNs that do not (always) fire in synchrony [41,75].

A particular example in the leech nervous system is the bilateral pair of electrically coupled MNs that control the activity of the pair of heart tubes. In line with the asymmetric activity of the heart tubes, these MNs receive asynchronic rhythmic input [76]. Experimental and modeling work suggests that the e-Syns influence both the intersegmental delay and the side-to-side phase difference throughout their rhythmic activity [77].

Interneuron to MN coupling was observed to mediate relevant physiological functions. In the motor network that controls prey capture in the mollusc Clione, a brief sensory stimulus is converted into a prolonged motor discharge that supports pursuing the motor task. This temporal conversion is performed through interneurons that are linked to the MNs via e-Syns and ch-Syns (Figure 2.A). When activated by a brief sensory stimulus the interneurons activate the MNs via excitatory ch-Syns, which in turn recursively activate the interneurons, generating a positive feedback that prolongs the active state [78].

Swimming in molluscs is controlled by a set of four interneurons linked by reciprocal inhibitory ch-Syns and ohmic e-Syns [79,80]. In several invertebrate systems it was observed that MNs are not mere output units of the central nervous system but form active part of networks that control rhythmic motor behaviors. Classical and extensively discussed examples are the pyloric rhythm in the crab digestive system and the leech swimming where it was found that MNs form part of the oscillatory networks and are linked to other units in the circuit by ch-Syns and e-Syns [68,81]. More recently
a similar picture was uncovered in the zebrafish, where MNs are electrically coupled to
excitatory interneurons that are part of the swimming motor pattern [82].

*Caenorhabditis elegans* exhibits rhythmic undulatory forward and backward locomotion. The
direction of movement is determined by interactions between specific forward and
backward motor circuits. Backward premotor neurons are linked to specific backward
MNs by ch-Syns and e-Syns; a similar connectivity was found for the forward circuit
(Figure 2.B). In spite of the apparent symmetry, a series of studies determined that e-
Syns in the backward network, but not in the forward one, play a key role in regulating
forward movement [83]. GJs function as shunts that decrease the excitability of the
premotor neurons that control backward MNs, establishing a bias for a higher forward
output.

As mentioned earlier, MNs can be electrically coupled promoting co-activity of
different muscles. However, muscle groups that function synergistically in one behavior
could act out of phase in another, and therefore coupling requires a fast control
mechanism. A circuitry was described in the nervous system of the leech where non-
synergistic MNs are widely coupled by ohmic e-Syns. The mechanism is centered on a
pair of premotor nonspiking (NS) neurons that are linked to every excitatory MN by
rectifying e-Syns and ch-Syns (Figure 2.C). The e-Syns is active when \( V_{mNS} < V_{MN} \);
and activation of MNs evokes a hyperpolarizing response in NS, mediated by ch-Syns.
As a consequence of this network the MN-MN interactions are counteracted [41,75].
For example, activation of MN-a will cause a direct excitatory signal onto MN-b
through the ohmic e-Syn that links them, and an inhibitory signal via NS. Excitation of
the MN is not transmitted to NS because of the rectifying nature of the junction, and
therefore the only effective signal transmitted to the other MNS via NS is inhibitory.
The two opposite signals cancel each other and no net change in \( V_{MN-b} \) is observed.
The network is effective when the nervous system displays a rhythmic motor pattern
compatible with crawling [84] and it was proposed, in addition, to function as a
recurrent inhibitory network [85].
Conclusions

E-Syns are fast means of communication that blur the cellular boundaries, generating fast and reliable routes of communication between neurons that are individual processing units. The sensory and motor networks described here illustrate circuitry motifs in which e-Syns provide, mostly, means of amplification. But as described in the *C. elegans* and leech nervous systems, given particular network configurations, it can serve as a fast and reliable inhibitory mechanism. The level of GJs expression can be certainly modulated in different physiological conditions, but while present in a circuitry, this intercellular link has a “quiet” but robust expression.
Figure Legends

Figure 1. Schematic representations that highlight the role of e-Syns in four different sensory systems. A. Terminals from auditory neurons are connected to the Mauthner neuron in the goldfish brain through ohmic e-Syns that allow bidirectionally symmetrical interactions. B. Mechanosensory terminals are connected to lateral giant interneurons in the terminal ganglion of the crayfish nervous system through rectifying e-Syns. In addition the mechanosensory neurons are interconnected by ohmic e-Syns. C. Tangential neurons extend their dendritic tree in the lobula plate of blowfly brains and are interconnected by ohmic e-Syns located at their axons. D. Specific odor receptor neurons contact projection neurons in specific glomeruli (represented as the rectangles delimited by pointed lines). Projection neurons innervating the same glomerulus are interconnected by ohmic e-Syns. In addition, excitatory interneurons span several glomeruli and are connected to projection neurons by e-Syns and ch-Syns.

Figure 2. Schematic representations that highlight the role of e-Syns in three different motor systems. A. Interneurons in the nervous system of Clione are connected to MNs innervating oral appendages involved in prey capture by e-Syns and ch-Syns. B. In C. elegans interneurons AVA and AVE (summarized as Ai) control MN A that produces backward movement, and interneurons PVC and AVB (summarized as Bi) control MN B that produces forward movement. Interneurons and MN are linked by ch-Syns and e-Syns. Interneurons are also interconnected by mixed synapses and MNs are interconnected by e-Syns. C. In the midbody ganglion of leeches the NS neuron is linked to MNs by rectifying e-Syns and MN produce disynaptic chemically mediated inhibitory responses onto NS. MNs are linked by relatively ohmic e-Syns.

Acknowledgments

The author thanks Dr. Fernando Locatelli for helpful discussion on olfactory systems and to Dr. Violeta Medan, Martín Carbó Tano and Fernando Locatelli for their comments. This work was supported by grant PICT 2012-0326 from Agencia de Promoción Científica y Tecnológica, MinCyT, Argentina.
References


These extensive review analyzes the structural complexity of gap junctions, their role in development, the effect of neuromodulators in their expression, and their involvement in pathobiology.


This report identifies and characterizes 9 new innexin genes in Hirudo verbana, a leech species highly used in physiological studies. It describes the expression of the 21 innexins identified in this species during development and in the adult nervous system, including the analysis in identified neurons.


Three-dimensional structural analysis of crystallized *C. elegans* innexin-6 gap junction channels determined that each one comprises 16 subunits, rather than the 12 subunits described for connexins.


A low threshold voltage activated calcium conductance boosts synaptic responses in a pair of nonspiking neurons of the leech. The homolog pair of neurons is electrically coupled and the calcium conductance aids the propagation of signals across electrical synapses.


This report describes the interactions of GABAergic projection neurons within the antennal lobes in Drosophila using dual-color calcium imaging. These neurons constitute an inhibitory feed forward path in the olfactory system, they receive direct inputs from olfactory receptor neurons, and, different than cholinergic projection neurons, they span multiple glomeruli, contacting cholinergic projection neurons with
mixed electrical and chemical synapses. Thus these neurons also provide to horizontal processing among different glomeruli and influence animal behavior.


A mechanism that grants intensity-invariant identification of odors is described in the zebrafish olfactory bulb. Interneurons linked via gap junctions and GABAergic synapses to mitral cells boost the responses to weak inputs and attenuate the responses to strong inputs, stabilizing the output activity patterns against variations in stimulus strength.


64. Poppele RBG: Sophisticated spinal contributions to motor control. TINS 2003, 26:269-276.


This report confirms in zebrafish that motoneurons can participate in motor control networks, as documented in several invertebrate systems. Motoneurons are linked to premotor neurons by electrical synapses and influence the generation of rhythmic activity.


This review summarizes a mechanism of recurrent inhibition uncovered in the leech nervous system and relates it to what has been described in vertebrates. The leech network is centered on a pair of nonspiking neurons that are linked to every excitatory motoneuron in the leech via chemical and electrical synapses. This network achieves two major effects: uncouples motoneurons linked by electrical synapses and controls the general level of motor activity throughout specific motor patterns.